UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

#6

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/297,092	05/18/99	PAULISTA M	P564-9010

HM22/1109

NIKAIDO MARMELSTEIN MURRAY & ORAM
METROPOLITAN SQUARE
655 FIFTEENTH STREET NW
SUITE 330 G STREET LOBBY
WASHINGTON DC 20005-5701

EXAMINER	
STROUP,C	
ART UNIT	**PAPER NUMBER**
1633	6
DATE MAILED:	11/09/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/297,092	Paulista et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-13 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-13 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 12 and 13 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 are unclear as to the meaning and properties of an osteoinductive versus osteogenetic sustance.

Claim 2 is unclear as to the metes and bounds of "fragments thereof". Which fragments provide the biological activity necessary to induce cartilage or bone growth.

Claim 3 is unclear as to the metes and bounds of the protein. What properties or biological activity denotes a "mature" protein and "essentially the same activity"? What other monomers and dimers from what other TGF-beta proteins when fused with SEQ ID NO: 1 provide a therapeutic effect upon implantation?

Claim 7 is unclear as to whether the release of A causes B degradation or the device is designed that they merely occur concurrently.

Claim 8 is unclear as to the metes and bounds of "appropriate solvent mixture".

Claim 11 is unclear as to the metes and bounds of "acceptable auxiliary substances".

Claims 12 and 13 are unclear due to the absence of steps for the process of making.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 2, 6-9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Urist et al (US Patent 4,596,574) .

Applicant's claimed invention is to a bioactive implant material and a pharmaceutical composition comprising said implant wherein the implant comprises an osteoinductive protein of the bone TGF beta superfamily, such as bone morphogenetic protein or fragments thereof, and an osteogenic matrix composed of a biodegradable beta-tricalcium phosphate ceramic which releases the TGF-beta protein in a controlled retarded manner and has a microporosity of 20-60% and pore sizes of 10-40 micrometers (claims 1,2,4,5, 7,); there may be diluents or fillers within the

pharmaceutical composition (claim 11), and be in an injectable suspension (claim 6). The claimed invention also includes a process of making and using said implant wherein the osteoinductive protein is applied to matrix with appropriate solvent mixtures in such a way that a homogeneous distribution of said protein in the microporous structure is achieved and is conducted through removal of the solvent via freeze drying; and the use of the implant or pharmaceutical composition for the treatment of bone defects (claims 8,11, and 12).

Urist, MR teaches the use of a biodegradable porous beta tricalcium phosphate ceramic matrix with bone morphogenetic protein (BMP) (col 2, lines 35-44) for the slow release of said protein for the purpose of inducing new bone growth (abstract), and the additional additives or supplements may be included in the matrix such as antibiotics (col 3, lines 64-68). Urist, MR also teaches a method of making said matrix with BMP by contacting the porous ceramic with a liquid containing the BMP, then evaporating the solvent through freezing drying while entrapping the BMP within the pores of the ceramic (col 3, lines 45-65, & claims 17-18), and leaving the composition in a liquid, hence injectable form which may be shaped as desired (col 4, lines 13-15). Urist also discloses the use of said matrix for the repair of bone in extraskeletal and intraskeletal sites (col 4, lines 40-45). Therefore, the claimed invention was clearly anticipated.

7. Claims 1, 2, 4, 5, 7, 8,10, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Oppermann et al (WO 91/05802).

Applicant's claimed invention is to bioactive implant material and a pharmaceutical composition comprising an osteoinductive protein of the bone TGF beta superfamily, such as bone morphogenetic protein or DNA, and a osteogenic matrix composed of a biodegradable beta-tricalcium phosphate ceramic which releases the TGF-beta protein in a sustained release manner, while causing no giant cell or connective tissue infiltration. The claimed invention is also to method of use of said implant for the treatment of disease and defects affecting bone such as

periodontosis, fractures, and replacements. The claimed invention also includes a process of making said implant wherein the osteoinductive protein is applied as a solution and concentrated in the osteogeneic matrix by in situ precipitation comprising admixing a precipitating solvent, such as water or ethanol, to the matrix.

Oppermann et al teach a biodegradable, biocompatible matrix and a method of making such comprising the fabrication of a recombinant protein or DNA into the pores of said matrix, wherein the pore size is from 1-100 micrometers (claim 21). The implant is biocompatible due to the removal of immune stimulating epitopes (pg 7, para 3), and therefore is unable to elicit a giant cell or connective tissue infiltration. Oppermann also teaches a method of making an osteogenic device comprising a biodegradable matrix of type I insoluble bone collagen wherein recombinantly produced osteogeneic homodimeric proteins such as OP1-16V (claim 2) are interspersed within the pores of the matrix via ethanol precipitation (pg 51, para 1) and released from the matrix in a sustained release manner (pg 44, para 4). Said matrix is utilized for the repair of orthopedic, periodontal, and reconstructive procedures (pg 44, para 4). Therefore, the claimed invention was clearly anticipated. (It is noted that the pore size and microporosity measured as a percent volume is a result effective variable which one of ordinary skill could modify.)

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urist et al (US Patent 4,596,574) in view of Oppermann et al (WO 91/05802) and Hoetten et al (10/94 Accession JC2347).

Applicant's claimed invention is to a bioactive implant material and its use in a pharmaceutical composition comprising an osteoinductive protein of the bone TGF beta superfamily, such as a bone morphogenetic protein, and a osteogenic matrix composed of a biodegradable beta-tricalcium phosphate ceramic which releases the TGF-beta protein or DNA in a controlled retarded manner. Said protein may be cartilage inducing and comprise the mature, modified N-terminus and functional parts of SEQ ID NO: 1, or be substitued by corresponding sequences from other vertebrates, and may also contain monomers or dimers from other TGF-beta proteins. Said pharmaceutical composition may also have diluents or fillers and be in an injectable suspension. The claimed invention also includes a process of making said implant wherein the osteoinductive protein is applied to the matrix with appropriate solvent mixtures in such a way that a homogeneous distribution of the protein in the microporous structure is achieved and is conducted through removal of the solvent via freeze drying or ethanol precipitation.

Urist, MR teaches the use of a biodegradable porous beta tricalcium phosphate ceramic matrix with bone morphogenetic protein (BMP) (col 2, lines 35-44) for the slow release of said protein for the purpose of inducing new bone growth (abstract), and the additional additives or supplements may be included in the matrix such as antibiotics (col 3, lines 64-68). Urist, MR also teaches a method of making said matrix with BMP by contacting the porous ceramic with a liquid containing the BMP, then evaporating the solvent through freezing drying while entrapping the BMP within the pores of the ceramic (col 3, lines 45-65, & claims 17-18) leaving the composition in a liquid form which may be shaped as desired (col 4, lines 13-15). Urist et al does not teach the use of cartilage inducing growth factors or ethanol precipitation.

Oppermann et al teach a matrix and a method of making an osteogenic device comprising a biodegradable matrix of type I insoluble bone collagen with a pore size from 1-100 micrometers (claim 21) which is also biocompatible

due to the removal of immune stimulating epitopes (pg 7, para 3), and wherein a recombinantly produced osteogeneic homodimeric proteins such as OP1-16V (claim 2) is interspersed within the pores of the matrix via ethanol precipitation (pg 51, para 1) and released from the matrix in a sustained release manner (pg 44, para 4). Said matrix is utilized for the repair of orthopedic, periodontal, and reconstructive procedures (pg 44, para 4). Oppermann et al also teach the make and use of recombinant proteins that have a modified N-terminus and are fusion proteins with sequences from proteins of the same family (pg 16, para 1).

Hoetten et al teach the identification of transforming growth factor differentiation 5, a cartilage-derived morphogenetic protein which has 100% identity to SEQ ID NO: 1. (Accession JC2347).

In light of Urist, Oppermann, and Hoetten et al it would have been obvious to one of ordinary skill in the art to make and use a device comprising an osteogeneic matrix and a osteoinductive or cartilage inductive protein with a modified N-terminus of SEQ ID NO: 1 and fusion with another TGF-beta protein; and to make said device utilizing ethanol precipitation or freeze drying. One would be motivated to do this to deliver a growth factor in a time release controlled manner to a tissue in need of repair or regeneration of cartilage (Hoetten et al) or bone (Urist,abstract); and because the use of ethanol precipitation or freeze drying were standards in the art of forming a matrix with a therapeutic protein (Urist, col 3, lines 45-65, & Oppermann et al, pg 51, para 1) . There would be a reasonable expectation of success because of Oppermann's et al and Urist's demonstration of the ability to utilize modified growth factors seeded within the pores of a biodegradable matrix to regenerate bone (full patents), while Hoetten teaches that SEQ ID NO: 1 is a growth factor to regenerate cartilage. Therefore, it is reasonable to assume that the substitution of SEQ ID NO:1, or a modified and enhanced version of such, would result in cartilage regrowth enhancement. (It is noted that the pore size and microporosity measured as a percent volume is a result effective variable which one of ordinary skill could modify.)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, can be reached at (703) 308-2035. The fax phone number for this Group is (703) 308-0294.

Carrie Stroup

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800